

stated that Ben-Haim et al teach a method of modifying the force of contraction of a heart by applying a non-excitatory electrical field (col. 1 @ 31-45) to modify alter/remodel the action potentials, the ionic pumps and the channels of the heart, hence preventing arrhythmias such as ventricular fibrillation. (col. 8 @ 41-48)

The Examiner stated that the channels that connect the heart, read to include gap junction channels, are modified/remodeled by electrical stimulation (col. 2 @ 6-col. 3 @ 32; col. 27 @ 12-27 and 52-57; col. 31 @ 1-5). The Examiner stated while the gap junction channels are not specifically mentioned when Ben-Haim addresses the channels of the heart, it is inherent that the Ben-Haim et al. invention controls the gap junction channels as they are an essential component of the heart conduction system as noted in the record by Winslow et al. (US 5947899) (col. 5 @ 28-col. 6 @ 3; col. 6 @ 33-53).

The Examiner stated that the refractory periods are modified by electrical stimulation (col. 8 @ 3-5; col. 47 @ 37-45; col. 8 @ 66-col. 9 @ 3; col. 9 @ 15-19; col. 17 @ 26-35; col. 17 @ 45-46; col. 31 @ 26-31) and that the ion channels are modified by electrical stimulation (col. 26 @ 62-col. 27 @ 27; col. 27 @ 43-57; col. 31 @ 1-5).

The Examiner stated that mechanical and electrical changes in the heart occur over time as the heart is altered/remodeled (col. 9 @ 51-55; col. 38 @ 48-col. 39 @ 10). The Examiner stated that electrodes can be attached by sewing (col. 30 @ 9-12) and that electrodes can be placed in the heart or in vessels. (col. 37 @ 30-35; col. 40 @ 48-51 The Examiner stated that electrodes can be activated in pairs. (col. 37 @ 15-17).

The Examiner stated that applicant's arguments filed August 4, 2003 have been fully considered, but they are not convincing. The Examiner stated that the applicant argues Ben-Haim et al. does not teach exciting the heart, resulting in remodeling of gap junctions, altering the refractory periods, or inducing ion channel remodeling. The Examiner stated that Ben-Haim teach the heart is controlled/altered/remodeled using electrical stimulation (col. 1 @ 26-27), hence modifying the action potentials, the ionic pumps, and the channels of the heart. (col. 2 @ 6-col. 3 @ 32) The Examiner stated as to gap junction channels, the channels that connect the heart are remodeled using electrical stimulation; the channels are read to include gap junction channels. (col. 2 @ 6-col. 3 @ 32; col. 27 @ 12-27 and 52-57; col. 31 @ 1-5) The Examiner stated that while the gap junction channels are not specifically mentioned when Ben-Haim addresses the channels of the heart, it is inherent that the Ben-Haim et al. invention controls the gap junction channels as they are an essential component of the heart conduction system as noted in the record by Winslow et al. (US5947899) (col. 5 @ 28-col.6 @ 3; col. 6 @ 33-53)

The Examiner stated that refractory periods, refractory periods are altered by electrical stimulation. (col. 8 @ 3-5; col. 47 @ 37-45; col. 8 @ 66-col. 9 @ 3; col. 9 @ 15-19; col. 17 @ 26-35; col. 17 @ 45-46; col. 31 @ 26-31)

The Examiner stated that ion channels, ion channels are remodeled by electrical stimulation (col. 26 @ 62-col. 27 @ 27; col. 27 @ 43-57; col. 31 @ 1-5)

The Examiner stated that the applicant argued that since Ben Haim et al. only changes the muscle mass of the heart over time, changing muscle mass does not necessarily result in

remodeling the gap junction, altering the refractory period in the heart or inducing the ion channel remodeling. The Examiner stated that Ben-Haim et al. disclose methods to control and change the electrical and mechanic activity of the cardiac muscle cells that produce changes in the muscle mass and changes in the action potential plateau duration, the activation time, the activation sequence, the contractability and the conduction pathways of the cardiac segment, hence, the Examiner stated, Ben-Haim is read to remodel gap junctions, alter the heart refractory period and induce ion channel remodeling. (col 2 @ 6-col. 3 @ 32; col. 7 @ 65-67; col. 34 @ 28-34)

The Examiner stated that the applicant asserts the Examiner interprets "ion channels" to include "gap junctions." The Examiner stated that she recognizes "ion channels" and "gap junctions" are different physiological entities.

The Examiner stated that in response to the applicant's argument that the reference fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. claim 20, 30, and 59-"the refractory period is altered, and remains altered after the external stimulation is removed") are not recited in the rejected claim(s). the Examiner stated that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

The Examiner stated that the applicant argues that Ben-Haim et al. only provides change and control of the cardiac processes in a current moment or until electrical stimulation ceases. The Examiner stated Ben-Haim et al. apply stimulation to create cardiac process changes in the

current moment. The Examiner stated that in addition, Ben-Haim et al. recognize applying electrical stimulation in the current moment produces long-term/permanent changes of the cardiac processes, read as remodeling and altering of the cardiac processes. The Examiner stated that these long-term changes are reflected in a need for the therapy to be altered periodically and are reflected when treatment targets are met and the therapy is discontinued because the cardiac process has been changed to the point that therapy is not longer needed, hence the Examiner stated, Ben-Haim et al disclose changes in the cardiac process in the moment and long-term. (col. 9 @ 15-19; col. 9 @ 51-col. 10 @ 3; col. 30 @ 34-37; col. 34 @ 15-38; col. 35 @ 55-59; col. 38 @ 48-col. 39 @ 18)

In response to the Examiner's assertion that it is inherent that the device in Ben-Haim's invention controls the gap junction channels as they are an essential component of the heart conduction system as noted in the record by Winslow et al., applicant asserts that Ben-Haim does not teach remodeling gap junction channels for the following reasons. Although the Examiner asserts that the device in Ben-Haim's invention controls the gap junction channels as they are an essential component of the heart conduction system as noted in the record by Winslow et al., Winslow et al. merely describe conductance models which can incorporate gap junctions. This does not mean that the device in Ben-Haim's invention would necessarily modify gap junction channels. The Examiner has not shown how altering ion channels automatically and necessarily includes modifying gap junctions. All excitable cells in the heart have a compliment of ion channels. These are transmembrane spanning proteins that communicate from inside the cell to

the extracellular space. They are complete, functional channels, having gating proteins and pores and having different segments (intra and extracellular domains as well as transmembrane-spanning domains having different amino acid sequences). They are not channel fragments. Each ion channel within a single cell is complete within itself. No additional cell is needed to complement or complete its structure or function.

A gap junctional protein existing in a single cell is not a channel. It is a hemichannel referred to as a connexon. Each connexion is made up of 6 connexins, which are identical protein sequences that surround a central pore. In order for a gap junctional channel to be made, two hemichannels, each coming from a different cell, must align across the extracellular space. Although these can transmit ions and small molecules like cyclic AMP, their major function is to transmit electrical current via a low-resistance intercellular pore that is made by each of the two hemichannels coming together. Hence, there is no complete gap junctional channel within a cell. It is a specialized structure contributed to equally by different cells.

Moreover, there are three types of connexins (Cx) in the heart: Cx43, 45, and 40. These are of different proportion in different parts of the heart (muscle, specialized conducting system, etc). Each has different conductance characteristics and yet each can contribute to the formation of gap junctions across cells. Transmembrane ion channels, which have many points of homology across calcium, potassium, and sodium channels, do not have these specialized connexin structures which constitute the

building blocks of gap junctions. Thus, because modifying the ion channels would not necessarily remodel the gap junction channels, and therefore, anticipate the claimed invention, applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

In addition, in response to the Examiner's assertion that Ben Haim teaches that electrical stimulation remodels ion channels and inherently remodels gap junctions, applicants state that the device in Ben Haim's invention would not necessarily remodel ion channels. Ben Haim's device applies an electrical field to the heart that does not cause the heart to be excited and activated. Rather, the device is simply used to modify the plateau currents, resulting in what is claimed to be an increase in force of contraction. In contrast, the presently claimed invention in the subject application applies an electrical stimulus to the heart that does excite it, resulting in altered activation, which must occur for the downstream channels to occur in gap junctions and ion channels. Because the device in Ben Haim's invention would not cause the heart to be excited, resulting in altered activation, his device would not necessarily induce ion channel remodeling or remodel gap junctions. Furthermore, the disclosure in Ben Haim is insufficient to demonstrate how the device in Ben Haim's invention would necessarily induce ion channel remodeling or that gap junctions would necessarily be remodeled. Thus, the device in Ben Haim would not necessarily induce ion channel remodeling or remodel gap junctions.

In response to the Examiner's assertion that refractory periods are altered by electrical stimulation, applicant asserts that the Ben Haim nowhere discloses that electrical stimulation would automatically alter the effective

refractive period (ERP), as claimed in the present application. In myocardium, ERPs are primarily determined by the recovery of excitability of sodium channels carrying the fast inward sodium current. This process is both voltage-and time-dependent. While ERP may change consonantly with action potential duration and QT interval, there is not an obligate 1:1 relationship. Thus, because the device in Ben Haim's invention would not necessarily alter refractory periods which is required to anticipate the claimed invention, applicants respectfully requests that the Examiner reconsider and withdraw this rejection.

In support of applicant's assertion that the device in Ben Haim's invention would not necessarily induce ion channel remodeling, remodel gap junctions, and alter the refractory period, applicants submit a declaration by Michael Rosen, M.D. which is attached hereto as **Exhibit 1**. In this declaration, Dr. Rosen explains that the device in the Ben Haim reference would not necessarily induce ion channel remodeling, remodel gap junctions, and alter the effective refractory period. Thus, applicant respectfully requests that the Examiner reconsider and withdraw these various grounds of rejection.

#### **Claim Rejections-35 U.S.C. §103**

The Examiner stated that claims 2, 5, 12, 13, 15, 21, 24, 31, 32, 34, 40, 43, 50, 51, 53, and 58-60 are rejected under

35 U.S.C. §103(a) as being unpatentable over Ben-Haim et al. in view of Edwards et al. (US 5681308)

The Examiner stated that as discussed in paragraph 2 of the action, Ben-Haim et al. disclose the claimed invention except for the 7cm x 1cm (claims 4, 23, and 42) strip (claims 2, 13, 21, 32, 40, and 51) of electrode material having linked multiple electrode pairs, where the pairs are arranged in two columns (claims 12, 31, and 50) with one electrode in each pair in one column and the other electrode in each pair in the other column (claims 5, 15, 24, 34, 43, 53, and 58-60).

The Examiner stated that Edwards et al. disclose an analogous mapping apparatus and teach that it is known to use a circuit (38) mounted on a membrane support (16) to serve as a cardiac electrode which provides columns of individually controlled treatment electrodes (34) which can be multiplexed to enable stimulation of electrode pairs. (figure 7; col. 7 @ 38-52) The Examiner stated that absent any teaching of criticality or unexpected results, it is understood the electrode can be configured as a 7cm x 1cm strip with only two columns of electrodes. The Examiner stated that the configuration changes is an obvious change in shape based on the specific application. The Examiner stated that, therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method for modifying the force of contraction of a heart as taught by Ben-Haim et al. with the electrode as taught by Edwards et al. to provide a flat electrode with multiple electrode measurement and stimulation configurations so the cardiac tissue can be more effectively treated.

The Examiner stated that claims 3, 4, 14, 17-19, 22, 23, 33, 36-38, 41, 42, 52, and 55-57 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ben-Haim et al. (US

6363279) in view of Edwards et al. (US5681308) and further in view of Dahl et al. (US5203348) The Examiner stated that as discussed in paragraphs 2 and 3 of this action, modified Ben-Haim et al. disclose the claimed invention except for:

- the electrode strip of polyurethane (claims 3, 14, 22, 33, 41, and 52),
- the electrode comprised of platinum or consisting essentially of unalloyed platinum (claims 17-18, 36-37, and 55-56), and the electrode connected to insulated stainless steel wire. (claims 19, 38, and 57)

The Examiner stated that Dahl et al. disclose an electrode and teach that it is known to fabricate an electrode with a platinum or platinum alloy conductor or conductor with a stainless steel core (col. 5 @ 19-36) and a lead with a medical grade polyurethane sheath and a stainless steel coated conductor. (col. 5 @ 23-38) The Examiner stated that therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the modified method for modifying the force of contraction of a heart as taught by Ben-Haim et al. with the materials of construction as taught by Dahl et al. The Examiner stated that one having ordinary skill in the art would have been motivated to make such a modification in electrode to specify materials of construction that have proven electrical properties.

The Examiner stated that claims 7, 8, 26, 27, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over

Ben-Haim et al. (US 6363279) in view of Dahl et al. (US 5203348) The Examiner stated that as discussed in paragraph 2 of this action, Ben-Haim et al. disclose the claimed invention except for the electrode being platinum or consisting essentially of unalloyed platinum.

The Examiner stated that Dahl et al. disclose an electrode and teach that it is known to fabricate an electrode with a platinum or platinum alloy conductor (col. 5 @ 23-38). The Examiner stated that therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method for modifying the force of contraction of a heart as taught by Ben-Haim et al., with the platinum of platinum alloy conductor as taught by Dahl et al. The Examiner stated that one having ordinary skill in the art would have been motivated to make such a modification in electrode to specify materials of construction that have proven electrical properties.

The Examiner stated that claims 6, 16, 25, 35, 44, and 54 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ben-Haim et al. in view of Edwards et al. and further in view of Ideker. The Examiner stated that as discussed in paragraphs 2 and 3 of this action, Ben-Haim et al. disclose the claimed invention except for the electrode pair being 2mm from each other and the electrode pairs being spaced at least 5 mm apart.

The Examiner stated that Ideker teaches a cardiac device for reducing arrhythmias and teaches that it is known to use an electrode configuration of an elongate primary strip with a plurality of electrodes positioned at spaced intervals, e.g. 1-4 millimeters (col. 3 @ 2-4). The Examiner stated that therefore, it would have been obvious to one having ordinary

skill in the art at the time the invention was made to modify the modified method for modifying the force of contraction of a heart as taught by Ben-Haim et al. with the electrode spacing as taught by Ideker to provide electrode spacing known to effectively reduce cardiac arrhythmias.

In response to the various grounds of obviousness rejections, applicants note that these rejections are based on the Ben Haim et al. reference in combination with at least one other reference and rely on the Ben Haim et al. reference as a primary reference. However, as discussed above, the Ben Haim et al. reference fails to teach or suggest any aspect of remodeling gap junctions, altering the refractory period in the heart, or inducing ion channel remodeling to prevent arrhythmias. The other references also fail to remedy the deficiencies of Ben Haim in this respect. Therefore, these proposed combinations necessarily fail to teach or suggest the claims against which they were cited. Moreover, applicant urges that there is no teaching or suggestion in the prior art or otherwise of anything that would motivate one of ordinary skill in the art to combine the references as proposed by the Examiner. Thus, applicant respectfully request that the Examiner reconsider and withdraw these various grounds of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Applicants: Rosen, et al.  
U.S. Serial No.: 09/505,458  
Filed: February 11, 2000  
Page 13

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White  
Registration No. 28,678  
Peter J. Phillips  
Registration No. 29,691  
Attorneys for Applicants  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, New York 10036  
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

 12/17/03  
Peter J. Phillips Date  
Reg. No. 29,691